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Webinar EVER Pharma

Innovative strategies to advance severe TBI treatment

October 12, 2021

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Webinar EVER Pharma (October 12, 2021)

Innovative strategies to advance severe TBI treatment

Participants

Johannes Vester

Head Biometry & Clinical Research, IDV Data Analysis and Study Planning, Gauting, Germany

Moderator

Topic: New vistas in TBI clinical research – on the way towards a new gold standard

Helmuth Trimmel

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Topic: Best supportive care in TBI: new hope based on combined neuroprotective treatments?

Ignacio Previgliano

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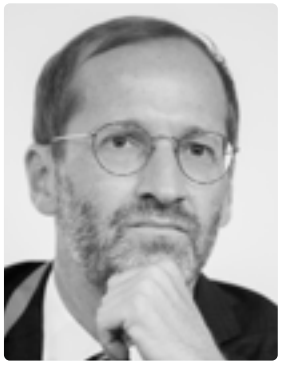
Topic: Post-intensive care syndrome: neurotrophic factor hypothesis



Peter Lackner

Head of Department of Neurology, Clinic Floridsdorf, Vienna, Austria

Topic: Innovative concepts for increasing awareness of multidisciplinary treatment after TBI

Order of the webinar

Introduction

Johannes Vester

Dr. Vester thanked EVER Pharma for organizing this multidisciplinary scientific meeting to update the audience on the most recent developments across the complex TBI care landscape. The primary goal of such a dedicated, focused initiative is to open our minds to innovative strategies for the future. That is what we needed in the very demanding field of TBI. This area of medicine faces many challenges which ought to be continuously addressed and critically revisited. The lecturers will discuss some of them from the standpoint of recent advances in clinical practice and research. In addition, the speakers will present various future-oriented and distinct perspectives. After this meeting, we hope to take home a broader understanding of the unmet needs in trauma management and a more profound knowledge of the developments in innovative care strategies. The topics include the updated preclinical and clinical concepts for treating severe TBI patients and the innovative educational approaches to establishing best care standards. Another subject of interest is the improved biometrical methodologies for solving the past clinical trial design failures that historically slowed down much-needed development in this complex therapeutic area.

New vistas in TBI clinical research – on the way towards a new gold standard

Johannes Vester

When discussing complex medical problems, like TBI, it is always instructive to look at historical development to understand significant challenges of the past, current solutions, and future perspectives. The groundbreaking methodology for TBI clinical trials was introduced around 2010 as a much-needed remedy for failing to approve any neuroprotective agent in the previous 30 years of research. Prominently, the statistical design flaws were blamed for these disappointing results. What were the critical methodological issues identified? The first concern was dichotomization of the outcome scales, usually GOS (Glasgow Outcome Scale, or its extended version, GOSE), featuring eight points describing the spectrum of outcome between death and complete recovery of a patient. This already low-resolution outcome scale was further compromised with the utilization of the statistical principle of dichotomous analysis. It cut the scale into two parts, one describing a favorable outcome and the second describing an unfavorable outcome. This approach dominated almost all past clinical trials in TBI and pre-determined their apparent futility to a large extent. For example, Dr. Vester was the responsible statistician for one of the major trials in this period, designed like that, investigating dexamethasone in acute brain injury.[1] Another example was cyclosporin A study, in which "For analytical purposes, the outcomes were dichotomized as a bad outcome (dead, vegetative, or severe disability) and good outcome (moderate disability or good recovery)".[2] The working research standard to assess and evaluate new treatments in TBI was the problem. The binary thinking dominated the field and dissociated clinical research from the biological reality and medical complexity of TBI (**Fig. 1**).

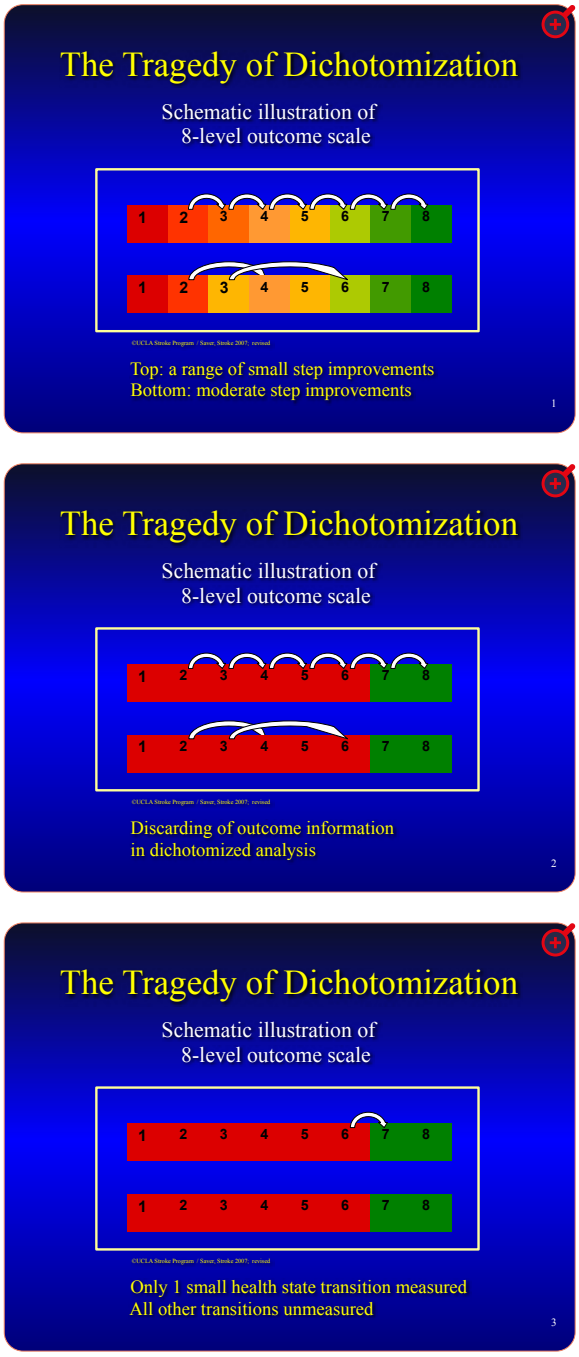


Fig. 1. The tragedy of dichotomization: how valuable clinical information is lost for research.

In effect, the researchers worked with an inadequate statistical tool that measured only one small transition in a patient's health status. In contrast, all other potential transitions (including moderate improvements that potentially significantly impact the quality of life of a patient and their family) were disregarded and lost for analysis. The problem was not specific for GOS. The same methodological paradigm was applied to all other outcome scales, like, for example, modified Rankin Scale (mRS) in stroke. It was unfortunate but also potentially harmful, as evidenced by the case of the ECASS II trial investigating the safety and efficacy of alteplase in ischemic stroke.[3] Here, the primary outcome measure was the mRS score of 0 to 1 at 90 days (a good outcome measure). The results of ECASS II were statistically insignificant, with p=0.277. However, a post-hoc analysis using an alternative definition of the good outcome, mRS score of 0 to 2, gave a statistically significant result, with p=0.024. The same patient population assessed in the same trial and analyzed using the same raw data gave contradictory results. The methodology used for the clinical trial can determine the success or failure of a new treatment in terms of its approval for clinical use. The first lesson learned was that the dichotomization approach is highly arbitrary and can lead to unreliable efficacy results. To eliminate this issue, one should use full outcome scales.

The next issue identified was the choice of the outcome scale. For more than 30 years, GOS was the leading efficacy endpoint in TBI trials. Was it adequate for such a complex disorder as TBI? If not, which scale should we favor? The dilemma involved choosing between GOS and cognitive function, motor function, anxiety/depression, and health-related quality of life (HRQoL) measures. Again, the choice seemed arbitrary, as all these clinical symptoms are essential parts of the clinical picture of TBI. To solve that dilemma, a novel approach was proposed in Europe and the United States. The IMPACT Recommendations for Improving the Design and Analysis of Clinical Trials in Moderate to Severe Traumatic Brain Injury stated that: "Outcome after TBI is by definition multidimensional including neurophysical disabilities and disturbances in mental functioning".[4] Similarly, the US Traumatic Brain Injury Clinical Trials Network stated: "Multiple measures are necessary to address the breadth of potential deficits and recovery following TBI".[5] The Traumatic Brain Injury Workshop Leaders: Prospective Recommendations 2009 added: "Single functional assessment scales are not able to identify important deficits".[6] In other words, instead of choosing just one of the assessment scales, we should use all of them and analyze the results using an appropriate statistical model.

How does the multidimensional approach change the design of the clinical trials? The idea is to assess the Global Status using different scales, for example, GOS, HADS (Hospital Anxiety and Depression Scale), and PSI (Processing Speed Index; for executive functions). Notably, the statistical analysis should account for potential similarities/overlaps between certain scales to eliminate the overestimation of specific parameters within the Global Status outcome, which is an inherent weakness of the simple composite score. It is accomplished by calculating the correlation or redundancy index of the employed scales. The leading correlation-sensitive approach for an ensemble of full scales is currently the Wei-Lachin procedure. The first successful application of this procedure dates back to 2000 when FDA approved a multiple sclerosis drug, Novantrone, based on results obtained through the directional Wei-Lachin test (**Fig. 2**).

Finally, a third of the discussed major hurdles to overcome in any TBI trial is a lack of the baseline outcome data – the issue related to the heterogeneity among the TBI population. That is why it is so difficult to measure the effect of any treatment in TBI trials; the study population must be comparable between the treatment arms. For this reason, the Baseline Prognostic Risk Score (BPRS) is a highly recommended tool for optimizing the study population when used in addition to Glasgow Coma Scale.[9] It is the first validated prognostic scale that takes into account factors recommended by the IMPACT group: age, motor score, CT, pupillary reactivity, hypoxia, hypotension, and traumatic subarachnoid hemorrhage (SAH). Tested in a group of 10 000 patients, it is also the first weighted prognostic model with proven generalizability.

In the field of TBI research, the CAPTAIN is the series of trials in which the proper multidimensional approach based on full outcome scales was applied for the first time (**Fig. 2**). The ensemble of nine outcome measures employed to evaluate the Global Status of a patient included: GOSE, PSI, Stroop VST, Color Trails Test (CTT), Digit Span (DS), Early Rehabilitation Barthel Index (EBI), Finger Tapping Test (FT), Mini-Mental Status Examination (MMSE), and HADS. The US TBI Working Group recommendations influenced the choice. The study population of the first CAPTAIN trial was well balanced (BPRS-optimized), and the results confirmed that the multidimensional approach could be successfully applied in TBI research (**Fig. 3**).

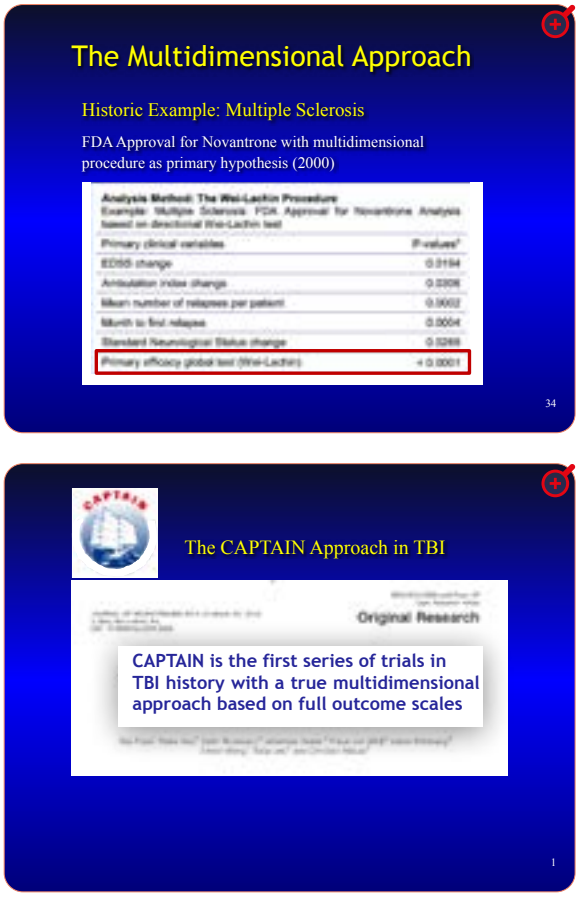


Fig. 2. The first FDA-approved drug evaluated using the primary efficacy global test with Wei-Lachin procedure, and the first application of this design principle for TBI study – the CAPTAIN trial series. [7,8]

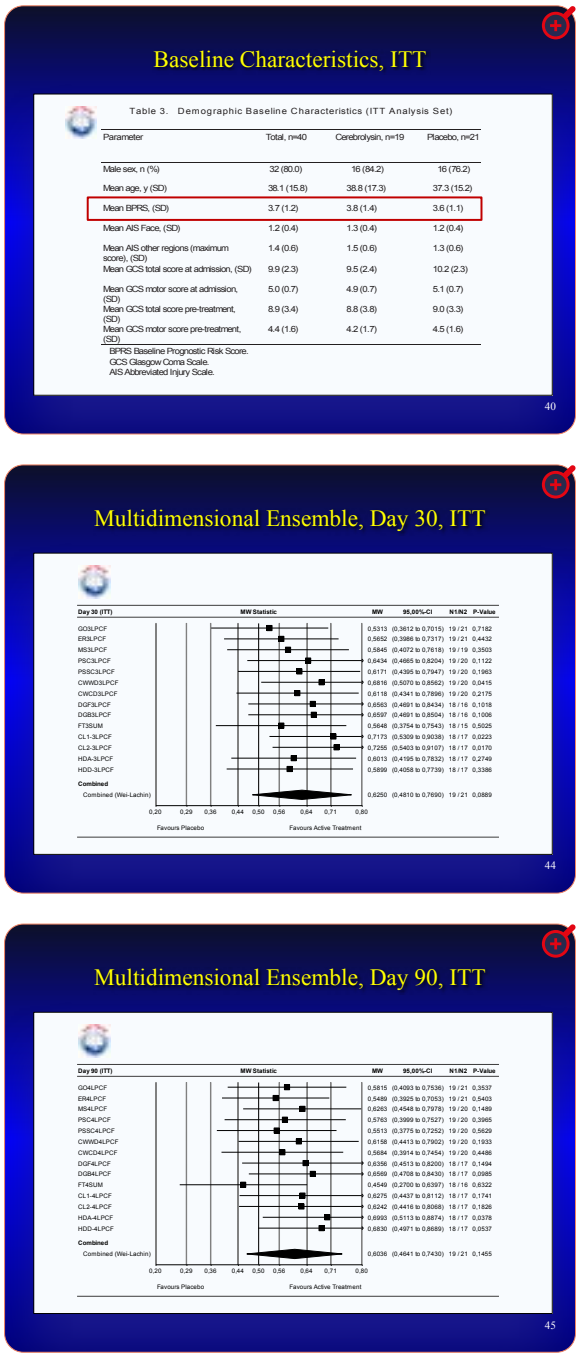


Fig. 3. The study population characteristics and the results of the CAPTAIN I trial.

This small trial's experience helped to identify the outcome measures most sensitive to the treatment with Cerebrolysin, including anxiety and depression scales. The trial also recorded the time-dependent character of the observed efficacy signals and, therefore, suggested the optimal observation periods for future studies. The CAPTAIN II trial included a larger population of TBI patients. The study groups were similar at baseline, as indicated by BPRS scores. Again, neuropsychological scales favored treatment with Cerebrolysin compared to placebo, while the Global Status assessed with the Wei-Lachin procedure indicated a statistically significant treatment effect of Cerebrolysin at day 90. The two trials were subsequently evaluated in the meta-analysis showing positive treatment effect of Cerebrolysin for the combined Global Status (Wei-Lachin) of the study populations at both day 30 and day 90 observation points (**Fig. 4**). The meta-analysis confirmed the excellent safety profile of Cerebrolysin in this susceptible and fragile patient population.[10]

Concluding his lecture, Dr. Vester underlined that multidimensional analysis offers a new direction for clinical and statistical thinking. This type of analysis appears to be more closely related to the complex nature of neurological disorders and outcomes than the previously established model used for several decades in TBI trials. This new concept was successfully tested in the CAPTAIN trials series and showed, for the first time, the beneficial effects of a neuroprotective agent after moderate to severe TBI. We should expect new positive developments in future TBI research as facilitated by this pioneering effort.

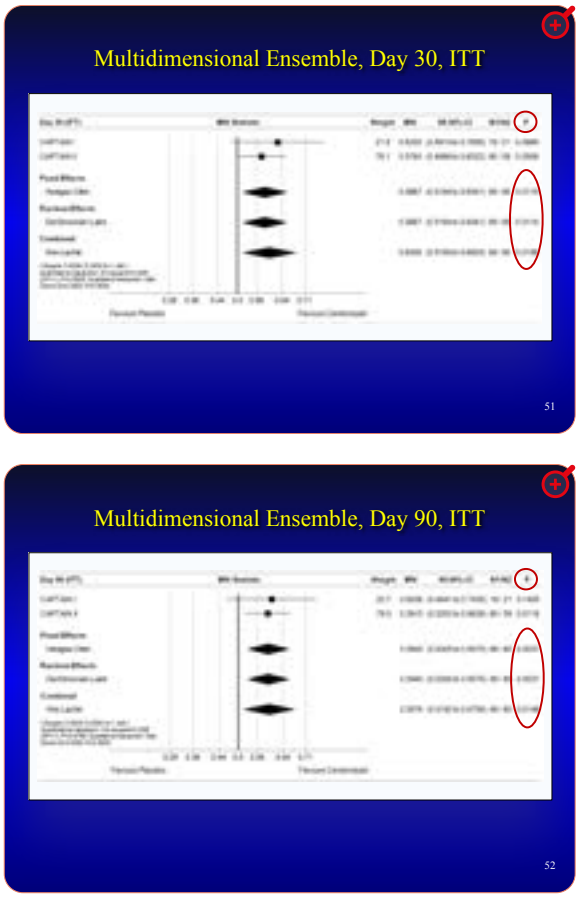


Fig. 4. The results of the meta-analysis of CAPTAIN I and II trials.

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Best supportive care in sTBI: New hope based on combined neuroprotective treatments?

H. Trimmel

The combined neuroprotective and neuroregenerative treatment in severe TBI is routinely practiced in Dr. Trimmer's clinic. Sharing this experience with the audience and anticipating future developments in TBI care were goals of Dr. Trimmer's presentation. TBI is often called "the silent epidemic." It affects mainly the population under 45 years of age, where it is the leading cause of death and disability. Depending on the world's region, the incidence of severe TBI is from 5 to 50 cases per 100 000 p/y. Trauma causes immediate/direct damage to the brain like bleeding, concussion, tissue depression, and diffuse axonal injury (DAI). More importantly, it triggers delayed/secondary damage, including ischemia/reperfusion, hypoxia, swelling, and infections. These delayed events are considered to be the main targets of neuroprotective and neuroregenerative interventions. Clinical research undertaken during the last two decades assessed agents like corticosteroids (CRASH trial, 2005), progesterone (SYNAPSE trial, 2014), cyclosporine A, erythropoietin, dexanabinol, statins, and magnesium.[1-7] The results were negative, or the reported therapeutic effects were unclear. The phase IIa study of the NO synthase inhibitor showed some positive anti-excitotoxicity effects leading to significant improvement in clinical outcome, however, at the expense of increased risk of kidney injury.[8] Despite past disappointments, new therapeutic opportunities can still be explored and tested, especially in monitoring, prevention, or limitation of secondary injuries in the early phases of TBI. Among them are Cerebrolysin and Citicoline. Cerebrolysin enhanced neurotrophic activity and neuroregeneration in animal models, reduced neuroinflammation, and blood-brain barrier (BBB) breakdown. It also showed benefits in moderate to severe TBI patients.[9-10] Citicoline impacts the reconstitution of cell membranes, enhances BBB integrity, and reduces edema in animal models. In clinical trials, it showed promising results: acceleration of consciousness recovery, improving outcome, and positive effects on mortality and cognitive recovery.[11-12]

Dr. Trimmel went on to present two instances where the combined neuroprotective/neuroregenerative approach was used to treat typical severe TBI patients in his clinical practice. The first patient, after a motorcycle accident, was treated with Citicoline 120 mg/h i.v. (3 g/50 ml NaCl; 2 ml/h), once at the ICU unit, for three weeks, according to already established internal protocol for managing severe TBI. Cerebrolysin treatment started late in this case – on day 31 (50 ml/day for 21 days) – a careful approach dictated by the fact that it was the first application of this therapy in the clinic and the patient was in a very bad condition. After ten days of Cerebrolysin treatment, the patient started reacting to verbal stimulation and was transferred to an open ward in the next few days. Considering the patient's status before Cerebrolysin treatment, the progress and the extent of recovery were remarkably fast. By the time the patient was transferred to a rehabilitation center, he was already completely awake and mobile in a wheelchair, followed simple commands, and answered questions adequately with a nod of the head. He spent six weeks in the rehabilitation center. After 12 month, the patient used a three-wheeld bicycle and currently even switched to a normal bike and undergoes a "fit-for-work" training program. This impressive level and speed of recovery surprised Dr. Trimmel and his team, considering this patient's initial severe status and unfavorable prognosis (**Fig. 1**).

A

W.S., 28 y, male student

B

W.S., 28 y, male student

Status on scene	**GCS 4**, pupils both narrow, **no reaction to light** BP 90/60, HR 80, SpO_2 92%, RF 16
Injuries	TBI III°, left serial rib fractures and pneumothorax, femoral neck fracture both sides fract. vert. TH XI – L II
Airway/Breathing Circulation	**ETI + CMV** on scene 500 mls HES, 1.000 mls cristalloid

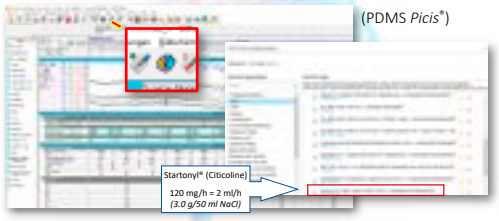
C

W.S., 28 y, male student

Status on arrival ER	GCS 3, pupils both narrow, no reaction to light BP 110/70, HR 85, SpO_2 99%, $etCO_2$ 34 mmHg
CCT scan	**punctiform cerebral haemorrhages** (esp. left temporal lobe), bilateral serial rib fractures and left scapular fracture, pneumothorax (drained), laceration + atelectasis of left lobe, fractures TH XI, XII, L1 + L4, both hip joints
Measures	ICP probe, art. line + CVC, ICU admission

D

sTBI – ICU treatment algorithm



E

W.S., 28 y, male student

ICU Course:	"***minimal handling***" for 10 days, followed by tracheostomy and nailing of the hips; prolonged weaning due to **vegetative instability**
MRI scan:	reveals **diffuse axonal trauma**: spotted susceptibility artifacts in the temporal lobe and frontobasal region (left > right) and basal ganglia, left posterior border zone and white matter on both sides. Multilocular shear haemorrhages, contusion zones in the left frontobasal and temporal region.
EEG:	general **diffuse brain dysfunction** (moderate to severe), reduced reactivity to photogenic stimuli, no epileptic potentials

Start with Cerebrolysin® on day 31

F

W.S., 28 y, male student

Day 41	patient **reacts targeted** to verbal stimulation
Day 45	transfer to **open ward** - awake and keeping eye contact, shows indicated movement when prompted with fingers and forearm
Day 73	**discharge from hospital**: awake and mobile in the armchair, follows simple commands, answers questions adequately with a nod of the head. Tetra paresis II-III°, pronounced on the left

After hospital discharge, patient spends further **6 weeks in rehabilitation center** ...

G

W.S., 28 y, male student

12 month after the accident ...

- in stable cognitive and mood state
- frequently using social media
- visiting friends and restaurants
- safely mobile by three-wheeled bicycle
- residual spasticity of right leg significantly regressed after botulinum toxin injections

Currently in a "*fit-for-work*" training program

Fig. 1. The severe TBI case nr. 1: A motorcycle accident resulting in diffuse axonal trauma. Phases of treatment: A-G

The second case concerned a severe TBI patient that fell from 300 m during the ski tour. The patient suffered multiple fractures throughout the body, apart from severe brain trauma. The scale and clinical picture of injuries led to the denial of the treatment by the University Hospital due to the perceived futility of the case. Accordingly, the patient was transferred for palliative care to Dr. Trimmel's clinic, which is in proximity to his home address. After discussion within the interdisciplinary team, the decision was made to try a maximum therapeutic approach instead of palliative care. After multiple surgeries, the patient was transferred to the ICU and treated according to the established protocols, supplemented by Citicoline (3 g/day) and Cerebrolysin (50 ml/day) for 21 days. That was the right decision. After a lengthy rehabilitation, the patient recovered very well, is mobile, and enjoys a good quality of life, back together with his family (**Fig. 2**).

A

2 F.P., 30 y sportsman

Fall from a height during ski tour

3 h from accident to HEMS rescue

Status on scene

- GCS 3, pupils both wide, minimal light reactive
- BP 88/60, HR 64, SpO_2 93, RF 8, t 34.4° C

Diagnosis by EP

- sTBI III°, multiple fractures of upper & lower extr.
- Serial rib fractures, fract. vert. C IV + sc injury

Measures: ETI + CMV on scene, fluids ...
airlifted to level II trauma center

B

F.P., 30 y, male

Status on scene: **GCS 3**, pupils both wide, minimal reaction to light
BP 88/54, HR 64, SpO_2 93%, RF 8, BT 33° C

Injuries: TBI III°, multiple fractures of upper and lower extremities,
serial rib fractures on both sides
fract. cervical spine, spinal cord injury

Airway/Breathing: ETI + CMV on scene
Circulation: 1.000 mls HES, 1.000 mls cristalloid

C

F.P., 30 y, male

CCT scan: cerebral contusions, subarachnoid (SAH) and subdural haemorrhage (SDH), unstable fracture corp. vert. IV with spinal cord lesion, rib fractures pneumothorax, multiple fractures upper and lower extremities.

Measures: external fixator, ICP probe, art. line + CVK, ICU admission

D

F.P., 30 y, male

Day 1 after trauma: haemodynamic and respiratory stabilized, surgeon decides for **plating and screwing** of the cervical spine and left hip

Postop CCT scan: increasing **brain oedema**, new **insult area** in posterior cerebral artery region caused by occlusion of the vertebral artery, **compression of the 4th ventricle** .

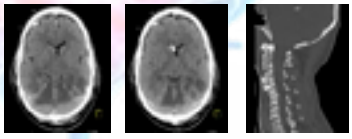
Transfer to university hospital: **denied** after assessment of CCT due to futility

Transfer to **Wiener Neustadt** (level III trauma center), intended for **palliative care** as the hospital is close to place of residence and relatives

E

F.P., 30 y, male

CCT on admission: oedematous swelling both cerebellar hemispheres and right occipital lobe, space-occupying effect in the posterior cranial fossa. Persistent dislocation fracture of vertebrae C4



F

F.P., 30 y, male

CCT on admission: oedematous swelling both cerebellar hemispheres and right occipital lobe, space-occupying effect in the posterior cranial fossa. Persistent dislocation fracture of vertebrae C4

Interdisciplinary case discussion with trauma and neurosurgeons, intensivist and radiologist – decision for **maximum therapeutic approach**

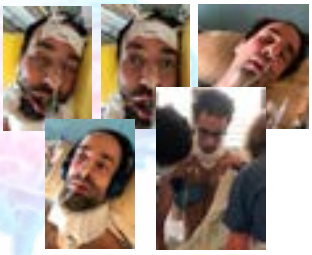
Surgery: placement of ventricular drainage, craniotomy with suboccipital decompression dural expansion plastic

ICU: treatment according to BTF guidelines, supplemented with Citicoline (3g/d) and Cerebrolysin (50 ml/d) for 21 d

G

F.P., 30 y, male

Prolongued ICU stay: day 1 - 45

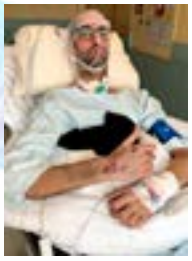


Pictures authorized by patient

H

F.P., 30 y, male

Prolongued ICU stay: day 46 - 55

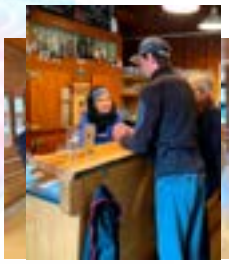


Pictures authorized by patient

I

F.P., 30 y, male sportsman

16 months after the accident ...



Pictures authorized by patient

Fig. 2. The severe TBI case nr. 2: A fall from a height during the ski tour. Phases of treatment: A-I

The complexity of the secondary brain damage after TBI is, in Dr. Trimmel's opinion, driven by two central underlying mechanisms. First, it relates to cell membrane failure. It triggers a cascade of events like excitotoxicity and activation of cell and tissue degrading enzymes (lipid peroxides, proteases, and phospholipases), leading to cellular apoptosis and further brain tissue damage. Another is dysfunction of the BBB, leading to migration of inflammatory agents (cells, plasma proteins, cytokines, cytotoxic proteins, ROS), activation of microglia, and resulting in neuroinflammation and edema. These processes start immediately but continue to expand during the initial weeks post-injury. It is therefore vital to initiate neuroprotective strategies within this timeframe. Up to date, several studies indicated beneficial effects of Citicoline related to its anti-oxidative stress action and anti-inflammatory properties. For Cerebrolysin, several clinical trials provided evidence for benefits in the cognitive domain and improved GOS scores. Moreover, the CAPTAIN II trial model proved to be a valid methodological blueprint for future clinical investigations. Treatment combination using these agents was investigated only once in a small study, which suggested that the beneficial effect measured with GOSE is more pronounced in the combination treatment group compared with the citicoline-only group, in mild to moderate TBI patients.[13] These results and the practical clinical experience of Dr. Trimmel's team provided a rationale for designing a new study (CITOLYSIN trial) investigating the efficacy and safety of the combined Citicoline-Cerebrolysin treatment in severe TBI patients (**Fig. 3**). The trial is under preparation and is expected to deliver results in about three years.

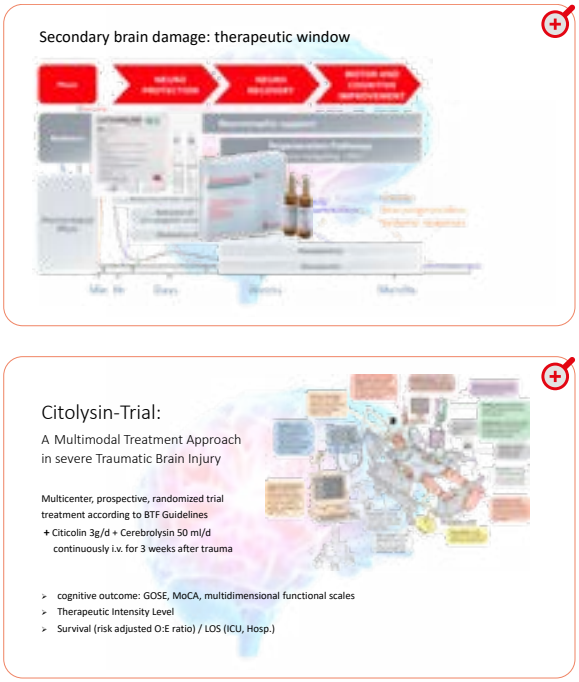


Fig. 3. The CITOLYSIN trial – testing a novel multimodal treatment approach in severe traumatic brain injury

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Post-intensive care syndrome: neurotrophic factor hypothesis

I. Previgliano

The subject of Post-Intensive Care Syndrom (PICS) is related to all critically ill patients. In patients suffering from severe TBI, its negative impact on recovery can often aggravate already poor prognosis. Dr. Previgliano has been interested in this topic since 2008/9 and summarised the neurotrophic hypothesis as a basis for a novel treatment approach in an article published a few years ago.[1] Today, his own experience with the PICS and newly published research allows for revisiting this idea. Dr. Previgliano discussed this topic in a few steps:

1. He characterized the clinical and pathophysiological picture of PICS.
2. He outlined the myokines concept as crucial for understanding the pathophysiological consequences of physical inactivity on neurological functions.
3. He showed how ICU-acquired weakness disturbs the neurotrophic regulation and contributes to the development of PICS.
4. He proposed a neurotrophic treatment strategy based on Cerebrolysin that targets the pathophysiological mechanisms underlying PICS development.

Dr. Previgliano also shared the results of his clinical investigations into the relationship between ICU-acquired weakness and cognitive decline.

The PICS is an example of secondary brain damage occurring independently of the primary brain damage. It consists of several components: ICU-acquired weakness (physical disability and impairment), new or worsened cognitive impairment, and neuropsychiatric disorders (depression, anxiety, PTSD). These three major components are the same things that also happen to TBI patients. PICS results in an enormous burden that includes productivity loss, excessive care costs (USD 15,022 – 34,515/patient/year), worsened quality of life, and permanent disability due to the element of cognitive impairment. There are several factors associated with PICS. The critical illness severity is the first factor manifesting itself with mechanical ventilation (for more than four days), shock, and trauma. Another one is the ICU-acquired weakness augmented by muscle relaxants and steroids. Finally, delirium is closely associated with PICS and is often triggered or exacerbated by sedatives (lorazepam) and analgesics (opioids). A recent study conducted by Dr. Previgliano and Dr. Mesa from Uruguay on a large ICU population showed that the incidence of PICS after 12 months is 37%. Among this population, 34% suffer from cognitive impairment. These results confirmed earlier observations by Pandharipande et al. (2013) and Mitchel et al. (2018).[2-3] It is important to remember that cognitive impairment after critical illness is independent of age, confirming its association with secondary brain damage. Regarding the level of cognitive impairment, it was found to be similar or worse than that occurring after moderate TBI or similar to mild Alzheimer's disease.

The most critical risk factor of PICS is delirium, an acute change in a mental status characterized by inattention and a fluctuating course. It is a brain failure that is highly prevalent in acutely ill patients, particularly those with a critical illness, among which up to 80% experience delirium. Longer duration of delirium was found to be an independent risk factor for worse RBANS global cognition scores at both 3 and 12 months after discharge ($p = 0.001$ and $p = 0.04$, respectively). It is therefore clear that delirium leads to brain damage. The damage manifests itself at the brain's tissue level as necrotic changes, hemorrhages, and axonal ruptures, all observed in patients with TBI and those without primary brain injury. Brain imaging can indicate brain atrophy, decreased volumes of the superior frontal lobes, thalami, cerebellum, and tractography alterations encompassing anterior internal capsule and knee of the corpus callosum (**Fig. 1**).

The prospective cohort study conducted in Latin American ICUs by Dr. Previgliano's team identified several factors influencing the onset of delirium in ventilated ICU patients.[4] For example, APACHE 19 score, mechanical ventilation of more than four days, steroids, tobacco smoke, alcohol consumption, psychiatric background, HIV positive, and mortality were all implicated in developing delirium. Something in this ICU population triggers delirium and then brain damage independent of primary brain injury.

What is the underlying pathophysiological mechanism? Finding the answer to this question should help in defining the treatment target(s) of PICS. First, we have to look into the relationship between the brain and the muscles. The muscles are a large endocrine organ and are considered a factory of neurotrophic factors (NTFs). The "myokines concept" explains that cytokines and other peptides (like NTFs) are produced, expressed, and released by muscle fibers and exert autocrine, paracrine, or endocrine effects. The receptors for myokines are found on muscle, fat, liver, pancreas, bone, heart, immune, and brain cells. The location of these receptors reflects the fact that myokines

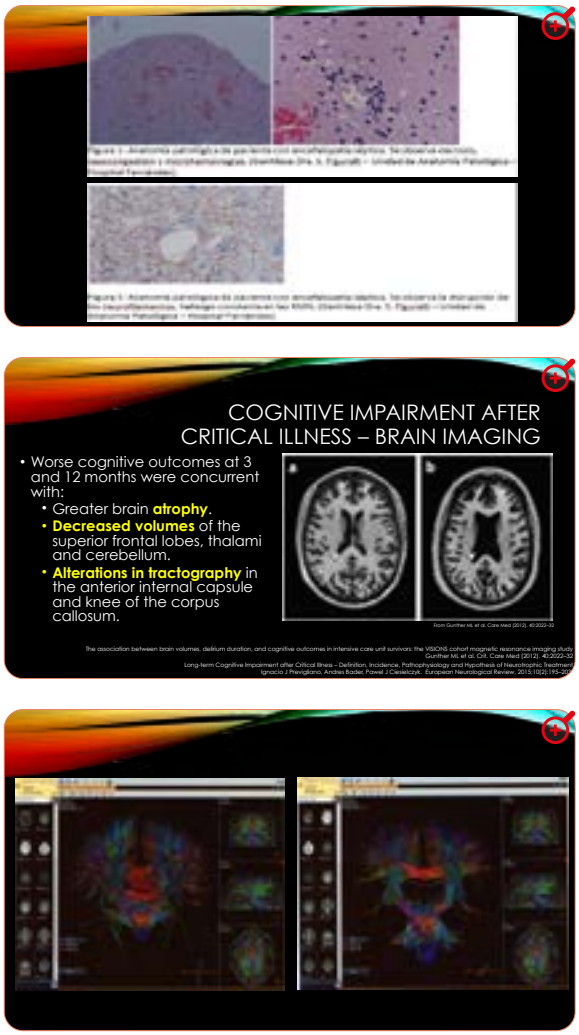

Fig. 1. Pathological changes observed in the brains of patients suffering from PICS

have multiple functions. They are involved in exercise-associated metabolic changes as well as in the metabolic changes following training adaptation. They also participate in tissue regeneration and repair, maintaining healthy bodily functioning, immunomodulation, cell signaling, expression, and differentiation. Therefore, the extreme physical inactivity of the ICU patient (especially the most vulnerable ventilated patient) is directly implicated in the development of PICS. The concept of diseasome of physical inactivity established by B.K. Pedersen identified type 2 diabetes, cardiovascular diseases, colon cancer, dementia, and depression as a cluster of diseases related to physical inactivity.[5] It overlaps with the clinical features of PICS. At the same time, most myokines act as neurotrophic factors, which are essential regulatory proteins of the central nervous system involved in the processes of neuroplasticity, neuroprotection, neuroregeneration, and neurorestoration. Among them, the brain-derived neurotrophic factor (BDNF) is one of the most important for normal brain functioning (**Fig. 2**).

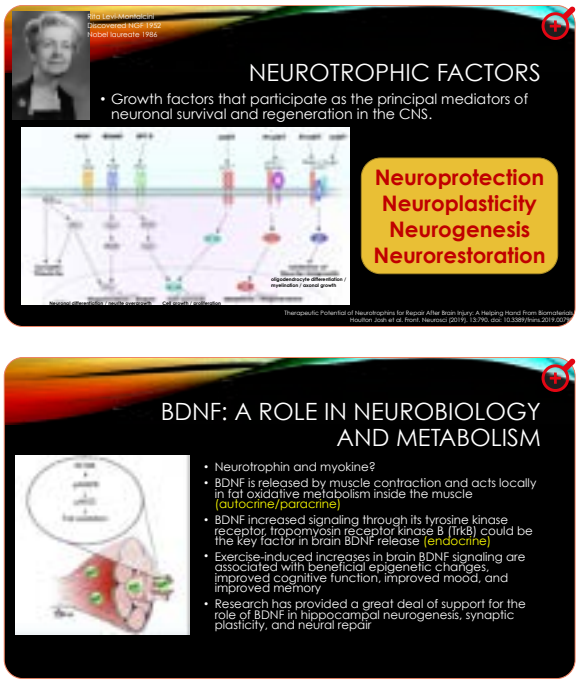

Fig. 2. The essential role of neurotrophic factors (NTFs) for neurobiology and metabolism

On the other hand, the increasing body of evidence confirms the essential role of physical activity in the normal functioning of the CNS. In a randomized controlled trial with 120 older adults, it was shown that the volume of the anterior hippocampus increased by 2% in response to aerobic training.[6] Aerobic exercise training increases grey and white matter volume in the prefrontal cortex of older adults and increases the functioning of key nodes in the executive control network. Greater amounts of physical activity have been associated with sparing prefrontal and temporal brain regions over nine years, reducing the risk for cognitive impairment. Hippocampal and medial temporal lobe volumes are larger in higher-fit older adults (larger hippocampal volumes have been demonstrated to mediate improvements in spatial memory). Exercise training increases cerebral blood volume and perfusion of the hippocampus, which partially explains observed beneficial effects. The causal relationship between physical inactivity and PICS was confirmed in recent years. Schweickert and coworkers (2009) examined the impact of early physical and occupational therapy in the ICU, starting with daily, passive range-of-motion exercises in heavily sedated patients and progressing to more advanced tasks as the patient's condition and functional status allowed.[7] In the intervention group, delirium was reduced by about 50% in terms of days with delirium and the duration of delirium. Importantly, current critical patient care guidelines (ABCDEF bundle) recommend early mobilization as the only intervention that has demonstrated a decrease in the days of delirium and incidence of PICS.[8]

The neurotrophic factor hypothesis states that critical illness leads to mechanical ventilation and immobility of a patient. This extremely passive state triggers delirium and brain failure due to disturbed neurotrophic regulation in the brain. As a consequence, the patient develops PICS and critical illness-associated cognitive impairment (**Fig. 3**).

In several studies conducted in ICU patients, Dr. Previgliano's group attempted to test the muscle's endocrine activity hypothesis. They found a close relationship between ICU acquired weakness, muscles inactivity, and cognitive deterioration.[9] Interestingly, the exact relationship has been confirmed in patients suffering from COVID-19 and admitted to ICU with neurological symptoms (n=67). Cognitive impairment was directly linked with the prevalence of ICU-acquired weakness, as was the decreased discharge rate from the IC unit and, subsequently, from the hospital. In addition, the incidence of delirium was closely associated with intracranial hypertension. These studies demonstrated a strong relationship between ICU-acquired weakness (muscles inactivity) and critical illness at ICU and the time of hospital discharge in COVID-19 and non-COVID-19 patients. Almost 52% of ventilated patients developed intracranial hypertension (ONS > 5.6 mm). Delirium was present in 59% of patients, and among patients with delirium, 93% had intracranial hypertension.

In conclusion, the studies investigating the relationship between the ICU-acquired weakness and PICS confirmed three significant categories of intervention that positively impact the clinical outcome of critically ill patients: awakening tests, physical exercise within the ICU, and cognitive and physical rehabilitation after ICU discharge. From the standpoint of the neurotrophic hypothesis, awakening the patient may release NTFs via cortical activation as cognitive rehabilitation does. At the same time, physical activity induces NTFs via the muscular trigger of NTFs liberation. Therefore, supporting these interventions with pharmacological neurotrophic treatment seems consequential for improving the outcomes in critically ill patients. That is the core of the neurotrophic hypothesis for treating critically ill patients to prevent and/or limit PICS.

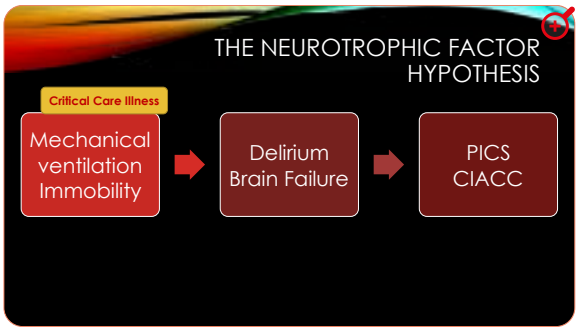

Fig. 3. The neurotrophic factor hypothesis explains the sequence of critical illness, immobility, delirium and PICS and suggests potential targets for novel pharmacological interventions

In this context, Cerebrolysin appears as a good candidate for the treatment of critically ill patients. It is already established in treating stroke, TBI, and dementia, indications that represent lesions that also occur in PICS patients. Moreover, it also has a well-established mode of action that significantly overlaps with the critical physiological functions of neurotrophic factors (i.a., neuroprotection, neuregeneration, neurogenesis, neurotrophicity). Importantly, it has confirmed a favorable safety profile in these most fragile groups of patients. Dr. Previgliano indicated that Cerebrolysin could be used in different phases of ICU care. Early treatment could support awakening tests and early mobilization at ICU. During the stay at a general ward, Cerebrolysin could be combined with physical and cognitive rehabilitation. After the hospital discharge, this agent could support continued physical and cognitive rehabilitation in a chronic intermittent administration model (**Fig. 4**).

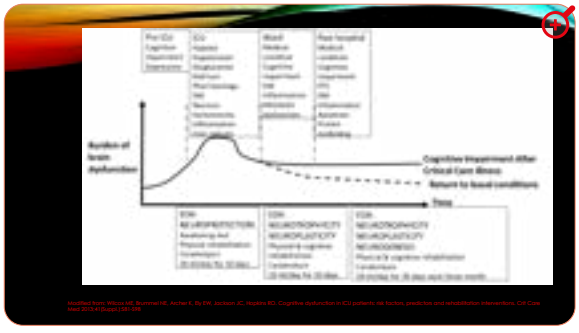

Fig. 4. The proposed treatment regimen with Cerebrolysin for prevention and treatment of PICS[1]

Anticipating this development, Dr. Previgliano's team has developed a clinical study protocol employing Cerebrolysin as a neurotrophic treatment. The study will evaluate the efficacy and safety of Cerebrolysin in the population of patients with COVID-19 hospitalized at ICU due to respiratory failure. The tested hypothesis states that supporting the standard care with a neurotrophic agent should help prevent deadly, overboarding cytokine storm and multi-organ failure while counteracting common physiological and psychological long-term effects of ICU stay, like PICS and lung fibrosis. Additionally, Cerebrolysin should serve as an effective treatment in cases of Covid-19-induced stroke. Finally, improved recovery of a patient should help in the suppression of virus amplification and mitigation of virus neuro-invasiveness. The treatment groups include, first, mechanically ventilated and, second, non-mechanically ventilated patients exposed to either standard of care or standard of care plus Cerebrolysin as add-on therapy. Primary efficacy criteria are cognitive batteries assessed at ICU discharge and then at follow-up visits at days: 30, 60, 90, 120, 180, and 360. The treatment spans the acute phase (30ml Cerebrolysin® IV for ten days) and the follow-up phase (each third-month intermittent cycle of 20ml Cerebrolysin for ten days, in an outpatient setting). The results are expected at the end of 2023.

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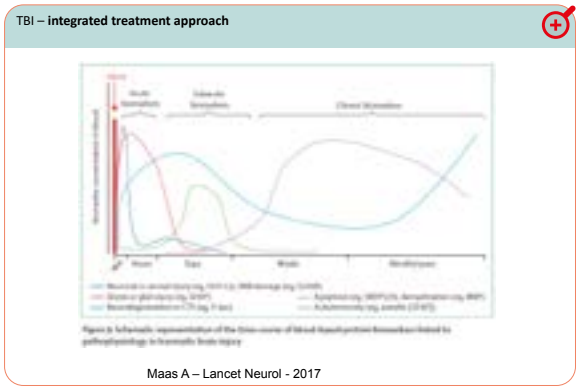
Innovative concepts for increasing awareness of multidisciplinary treatment after TBI

P. Lackner

Multidisciplinary care is of core value for the effective management and recovery of TBI patients. Therefore, increasing awareness of its advantages is much needed for improved implementation in clinical practice. TBI is a very complex disease, far more complicated than stroke, as seen in the pathophysiology of direct damage and its far-reaching and complex secondary consequences. The disentanglement of this complexity is a work in progress, with new biomarker research shedding more light in recent years, on the underlying mechanisms of potential value as treatment targets (**Fig. 1**).

These data indicate that the chain of care must not be limited to the initial weeks after the trauma but should be organized to allow for specific interventions to be administered in a long-term perspective. While this reality is well-recognized, it is still practically difficult to achieve a uniformly high standard of care between trauma centers, even if we refer to the early, acute stage of care. The CENTER-TBI study showed that the primary treatment goals, like initial oxygen saturation, initial PaO2, treating fever, treating/preventing seizures, or how a patient should be handled in case of increased intracranial pressure, vary significantly between TBI centers.[1] The question is, how can we overcome these discrepancies? Establishing the common care pathways is paramount. Next, the registries and extensive database studies help understand how to implement them in clinical practice and how to get closer to the gold standard (consensus). The missing link between the science and the execution of its findings in clinical practice can and should be addressed with educational programs and simulation centers. Here, the whole multidisciplinary team is the effort's target, not just one particular medical specialization.



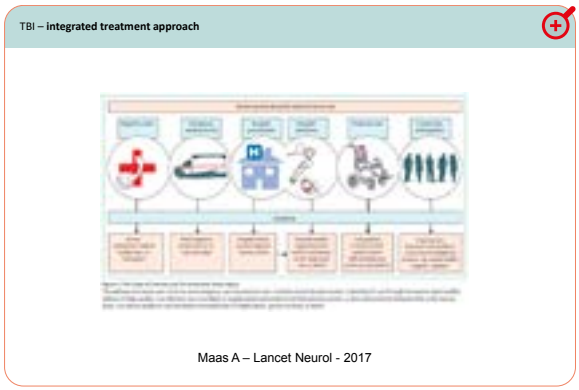


Fig. 1. The complex pathophysiology of TBI must be reflected in the proposed care pathways.

One successful example of care pathway that can also be emulated in TBI is the Tyrol Stroke Pathway. Dr. Lackner took part in its implementation in the years 2010-14. It shows significant overlaps with TBI care and includes pre-hospital, hospital, inpatient rehabilitation, and outpatient rehabilitation phases.[2] For each of the processes grouped in these major categories/phases, standard operating procedures were developed to establish a clear standard of care. All these SOPs were validated with a particular focus on the transition points between the phases of care, where much valuable information about a patient and time is usually lost. This stroke care pathway was implemented and subsequently validated with known/available quality indicators like the rate of thrombolysis. It went from 10% up to 20% during four year period of evaluation. Even the outcome (measured with mRS) gradually and steadily improved throughout the implementation period (**Fig. 2**).

Recently, a similar care pathway was proposed, by NHS, for TBI.[3] The vital crosstalk/transition areas between the phases of care were also addressed, including traditionally least controlled transition from inpatient to outpatient care.

Fig. 2. An example of a successful establishment of a care pathway – the Tyrol Stroke Pathway experience.

Building effective care pathways requires data. These are increasingly coming from large trauma registries, which were initially launched independently by many medical centers worldwide, and therefore displayed significant differences in complexity, data quality, and analyzed TBI populations.[4] Much needed harmonization has been undertaken by efforts like The IMPACT Study, IMPACT Database, and CRASH studies.[5] Currently, the International Initiative for Traumatic Brain Injury Research (InTBIR) coordinates these efforts and builds an extensive database through studies like TRACK-TBI or CENTER-TBI. The idea is to bring in as much data as possible and to make it accessible (exchangeable) and valuable (compatible) for analyses (**Fig. 3**). The next step would be the application of Artificial Intelligence for Big Data-type analyses.

The important goal right now is to develop or identify quality indicators that we can use to measure the effectiveness of our trauma care, suggested Dr. Lackner. Delphi Process is one example of such an endeavor in the area of ICU care.[6] In such a process, experts try to identify only those most essential quality indicators (through consensus). Not an easy task, but the overarching idea is to simplify our decision-making in the clinic. Between the large database registries like CENTER-TBI (stimulating discovery-driven analyses, creating evidence, identifying the standard of care) and raw data sourced from insurance claims (providing incidence and mortality statistics), there is a place for more specialized registries that collect quality indicators which allow for benchmarking and knowledge transfer. This realization led to the idea of creating the PRESENT (Patient REgistry, Short, Essential NeuroTrauma) (**Fig. 4**).

Fig. 3. Harmonization of databases for supporting data exchangeability and stimulating high quality research output in TBI.

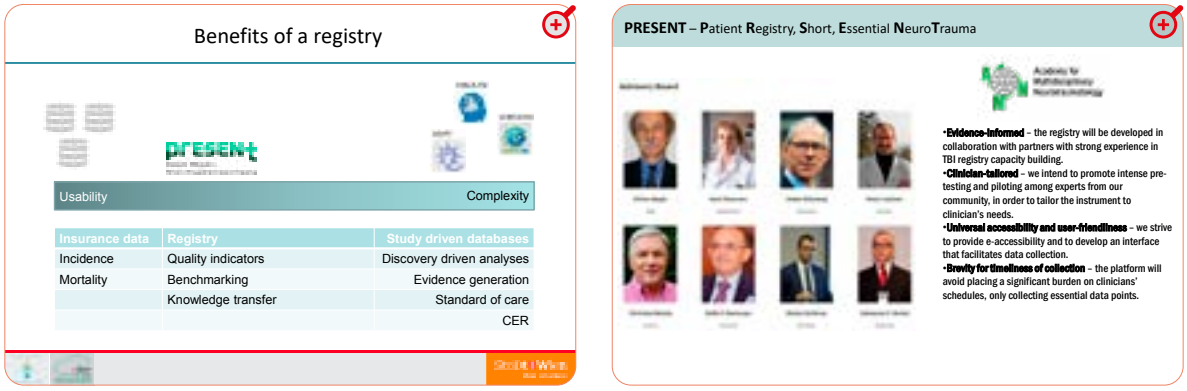


Fig. 4. The PRESENT aims at streamlining the registries data into a form of quality indicators for improved translation of knowledge into clinical practice of TBI care.

It is a project initiated in 2018 at The Academy for Multidisciplinary Neurotraumatology conference in Cluj, Romania. The target population of this registry are patients diagnosed with TBI (ICD-10) and admitted to a hospital. It is a user-friendly electronic platform with easy access and also easy to fill out. It collects only essential data and minimizes the time needed for entering the data. It also avoids a need for high-maintenance data surveillance system. Interestingly, in its current beta form, the platform is already active in real-time, allowing for benchmarking and comparisons between participating centers and countries. It also encourages participation with a reward system.

Dr. Lackner concluded his lecture by introducing the audience to yet another interesting educational program: TBI Treatment Simulation Centre Vienna. This project is under development, and its launch is planned for next year. The idea is to set up a simulation curriculum in Vienna where one can learn/practice along the whole chain of trauma care, at the level reflecting the current gold standard of TBI care in Austria. The center of Dr. Helmuth Trimmel will cover the acute trauma care; the general hospital will manage the neurosurgery part in Vienna under the supervision of Dr. Christian Matula, the neurology section (mainly mild-moderate TBI) will be supplied by Dr. Lackner and Clinic Floridsdorf, while Dr. Andreas Winkler and Klinik Bad Pirawarth will take care of the rehabilitation phase after TBI (**Fig. 5**).

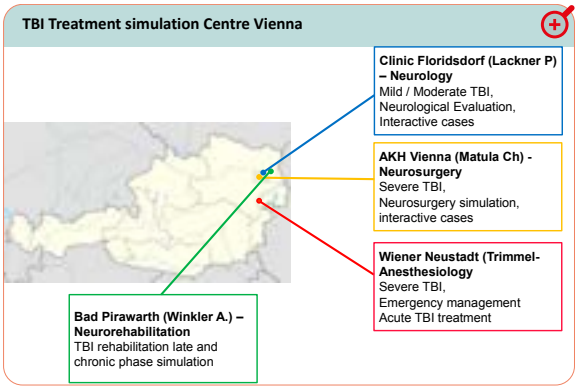


Fig. 5. The TBI Treatment Simulation Centre Vienna.

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ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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